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(54) Title: NOVEL MEDICAL USE OF SELECTIVE CB₁-RECEPTOR ANTAGONISTS

(57) Abstract: The present invention relates to a novel medical use of selective CB₁ receptor antagonistic compounds. Said com-
pounds are particularly suitable in the manufacture of medicaments for the treatment and/or prophylaxis of CB₁ receptor related
diseases in juvenile patients (pediatric treating), e.g. in particular obesity in juvenile patients, and/or for the treatment and/or pro-
phylaxis of drug induced obesity in juvenile as well as in adolescent patients. The CB₁ receptor antagonistic compounds suitable
according to the invention are elucidated in more detail in the description.

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NOVEL MEDICAL USE OF SELECTIVE CB₁-RECEPTOR ANTAGONISTS

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The present invention relates to novel therapeutic and/or prophylactic uses of selective CB₁-antagonists and to pharmaceutical compositions containing one or more of these compounds as an active component for the novel uses. The selective CB₁-antagonists addressed in this invention are potent Cannabis-1 (CB₁) receptor antagonists with outstanding utility for the novel medical uses provided by the present invention.

Cannabinoids are present in the Indian hemp *Cannabis Sativa L.* and have been used as medicinal agents for centuries (Mechoulam, R.; Feigenbaum, J.J. *Prog. Med. Chem.* **1987**, *24*, 159). However, only within the past ten years the research in the cannabinoid area has revealed pivotal information on cannabinoid receptors and their (endogenous) agonists and antagonists. The discovery and the subsequent cloning of two different subtypes of Cannabinoid receptors (CB₁ and CB₂) stimulated the search for novel cannabinoid receptor antagonists (Munro, S.; Thomas, K.L.; Abu-Shaar, M. *Nature* **1993**, *365*, 61. Matsuda, L.A.; Bonner, T.I. *Cannabinoid Receptors*, Pertwee, R.G. Ed. **1995**, 117, Academic Press, London). In addition, pharmaceutical companies became interested in the development of cannabinoid drugs for the treatment of diseases connected with disorders of the cannabinoid system. The wide distribution of CB₁ receptors in the brain, in combination with the strictly peripheral localisation of the CB₂ receptor, makes the CB₁ receptor a very interesting molecular target for CNS-directed drug discovery in the areas of both psychiatric and neurological disorders (Consroe, P. *Neurobiology of Disease* **1998**, *5*, 534. Pop, E. *Curr. Opin. In CPNS Investigational Drugs* **1999**, *1*, 587. Greenberg, D.A. *Drug News Perspect.* **1999**, *12*, 458). Hitherto, three types of distinct CB₁ receptor antagonists are known. Sanofi disclosed their diarylpyrazole congeners as selective CB₁ receptor antagonists. A representative example is SR-141716A, which is currently undergoing Phase II clinical development for psychotic disorders (Dutta, A.K.; Sard, H.; Ryan, W.; Razdan, R.K.; Compton, D.R.; Martin, B.R. *Med. Chem. Res.* **1994**, *5*, 54. Lan, R.; Liu, Q.; Fan, P.; Lin, S.; Fernando, S.R.; McCallion, D.; Pertwee, R.; Makriyannis, A. *J. Med. Chem.* **1999**, *42*, 769. Nakamura-Palacios, E.M.; Moerschbaeher, J.M.; Barker, L.A. *CNS Drug Rev.* **1999**, *5*, 43). Aminoalkylindoles have been disclosed as CB₁ receptor antagonists. A

representative example is lodopravadoline (AM-630), which was introduced in 1995. AM-630 is a CB₁ receptor antagonist, but sometimes behaves as a weak partial agonist (Hosohata, K.; Quock, R.M.; Hosohata, Y.; Burkey, T.H.; Makriyannis, A.; Consroe, P.; Roeske, W.R.; Yamamura, H.I. *Life Sc.* **1997**, *61*, PL115). More recently, researchers from Eli Lilly described aryl-aryl substituted benzofurans as selective CB₁ receptor antagonists (e.g. LY-320135) (Felder, C.C.; Joyce, K.E.; Briley, E.J.; Glass, M.; Mackie, K.P.; Fahey, K.J.; Cullinan, G.J.; Hunden, D.C.; Johnson, D.W.; Chaney, M.O.; Koppel, G.A.; Brownstein, M. *J. Pharmacol. Exp. Ther.* **1998**, *284*, 291). Recently, 3-alkyl-5,5'-diphenylimidazolidinediones were described as cannabinoid receptor ligands, which were indicated to be cannabinoid antagonists (Kanyonyo, M.; Govaerts, S.J.; Hermans, E.; Poupaert, J.H.; Lambert, D.M. *Biorg. Med. Chem. Lett.* **1999**, *9*, 2233). Interestingly, many CB₁ receptor antagonists have been reported to behave as inverse agonists *in vitro* (Landsman, R.S.; Burkey, T.H.; Consroe, P.; Roeske, W.R.; Yamamura, H.I. *Eur. J. Pharmacol.* **1997**, *334*, R1). Recent reviews provide a nice overview of the current status in the cannabinoid research area (Mechoulam, R.; Hanus, L.; Fride, E. *Prog. Med. Chem.* **1998**, *35*, 199. Lambert, D.M. *Curr. Med. Chem.* **1999**, *6*, 635. Mechoulam, R.; Fride, E.; Di Marzo, V. *Eur. J. Pharmacol.* **1998**, *359*, 1). From the international patent application WO 01/70700 4,5-dihydro-1H-pyrazole compounds are known which exhibit potent and selective cannabis CB₁-receptor antagonistic activity.

It is an objective of the invention to provide improved methods of treatment and/or prophylaxis which are particularly suitable in patient groups with enhanced need of safety and tolerability, e.g. in the treatment of obesity patients, in particular such as juvenile obesity patients and/or patients subject to long term treatment, e.g. in drug induced obesity in juvenile or adolescent patients.

It has now surprisingly been found that selective CB₁-antagonists in general, prodrugs thereof, tautomers thereof and salts thereof, show a unique pharmacological profile and therefore are particularly suited for the use in the manufacture of a medicaments for the treatment and/or prophylaxis of obesity patients, in particular of obesity in juvenile patients and/or drug induced obesity in juvenile, as well as adolescent, patients. In this regard selective CB₁-antagonistic compounds are highly valuable in providing medicaments for paediatric use on the one hand, and for the general use in drug induced obesity.

The term "selective" means that preferably there is no substantial other activity

than the CB₁-receptor antagonistic activity, or that at least the CB₁-receptor antagonistic activity is substantially overcompensating any other activity.

5 The outstanding unique pharmacological profile of selective CB₁-antagonistic compounds includes particularly high safety and tolerability which make the compounds particularly suitable in patient groups with enhanced need of safety and tolerability, in particular such as juvenile patients and/or patients subject to long term treatment, e.g. in drug induced obesity.

10 Due to the potent and selective CB₁ antagonistic activity the compounds used according to the invention are suitable also for use in paediatric treatment and/or prophylaxis of other disorders than juvenile obesity and drug induced obesity in juvenile patients. The other disorders include those known from the literature for the concerned selective CB₁ antagonistic compound, e.g. paediatric treatment
15 and/or prophylaxis may pertain to psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders and appetite disorders, neurological disorders such as dementia, dystonia, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, as well as for the treatment of pain disorders and other CNS-
20 diseases involving cannabinoid neurotransmission, and in the treatment of gastrointestinal disorders and cardiovascular disorders, in young patients.

The whole content of the literature mentioned in the description of the present invention is incorporated by reference into the present application.

25 The selective CB₁ antagonistic compounds used in the present the invention can be obtained according to known methods. Suitable ways of synthesis for the compounds used according to the present invention are described in the state of the art, e.g. in the documents cited in the present application and incorporated by
30 reference.

Examples of selective CB₁ antagonistic compounds being relevant in the context of the present invention and incorporated by reference are for example (but not being limited thereto):

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- 1) Diarylpyrazole congeners disclosed by Sanofi as selective CB₁ receptor antagonists, e.g. as representative example the compound SR-141716A, rimonabant and related compounds described e.g. in EP 0969835, SR-147778, SR-140098 (Central mediation of the cannabinoid cue: activity of

- a selective CB1 antagonist, SR 141716A Perio A, Rinaldi-Carmona M, Maruani J Behavioural Pharmacology 1996, 7:1 (65-71)); WIN-54461 disclosed by Sanofi-Winthrop (Cannabinoid receptor ligands : Clinical and neuropharmacological considerations relevant to future drug discovery and development. Pertwee RG, Expert Opinion on Investigational Drugs 1996, 5:10 (1245-1253))
- 2) Aminoalkylindoles having been disclosed as CB₁ receptor antagonists, e.g. as a representative example the compound Iodopravadoline (AM-630),
- 3) Aryl-aryl substituted benzofurans described by Eli Lilly as selective CB₁ receptor antagonists, e.g. LY-320135 (Cannabinoid receptor ligands : Clinical and neuropharmacological considerations relevant to future drug discovery and development. Pertwee RG, Expert Opinion on Investigational Drugs 1996, 5:10 (1245-1253)),
- 4) Compounds described by Merck & Co, e.g. AM 251 and AM 281 (Conference: 31st Annual Meeting of the Society for Neuroscience, San Diego, USA, 10-15.11.2001), and substituted imidazolyl derivatives disclosed e.g. in US 2003-114495 or WO 03/007887,
- 5) Azetidine derivatives described by Aventis Pharma e.g. in WO 02/28346 or EP 1328269,
- 6) CP-55940 from Pfizer Inc. (Comparison of the pharmacology and signal transduction of the human cannabinoid CB1 and CB2 receptors, Felder CC, Joyce KE, Briley EM, Mansouri J, Mackie K, Blond O, Lai Y, Ma AL, Mitchell RL, Molecular Pharmacology 1995, 48:3 (443)),
- 7) Diaryl-pyrazine-amide derivatives from Astra Zeneca described e.g. in the WO 03/051851,
- 8) ACPA and ACEA from Med. Coll. Wisconsin (Univ. Aberdeen), ("Effects of AM 251 & AM 281, cannabinoid CB1 antagonists, on palatable food intake in lewis rats" J.Pharmacol.Exp.Ther. 289, No3, 1427-33, 1999),
- 9) Pyrazole derivatives described by the University of Connecticut e.g. in the WO 01/29007,
- 10) HU-210 (International Association for the Study of Pain - Ninth World Congress (Part II) Vienna, Austria, Dickenson AH, Carpenter K, Suzuki R, IDDB MEETING REPORT 1999, August 22-27) and HU-243 (Cannabinoid receptor agonists and antagonists, Barth F, Current Opinion in Therapeutic Patents 1998, 8:3 (301-313)) from Yissum R&D Co Hebrew Univ. of Jerusalem,
- 11) O-823 from Organix Inc. (Drug development pipeline: O-585, O-823, O-689, O-1072, nonamines, Orgaix, Altropane Organix Inc, Company

Communication 1999, August 10; IDDb database) and O-2093 from Consiglio Nazionale delle Ricerche ("A structure/activity relationship study on arvanil, endocannabinoid and vanilloid hybrid.", Marzo DV, Griffin G, Petrocellis L, Brandi I, Bisogno T, Journal of Pharmacology and Experimental Therapeutics 2002, 300:3 (984-991)),

12) 3-Alkyl-5,5'-diphenylimidazolidinediones which were described as cannabinoid receptor ligands,

13) CB₁ antagonistic compounds currently under development by Bayer AG (IDDb database: company communication 2002, February 28).

The CB₁ antagonistic compounds used according to the invention can be brought into forms suitable for paediatric administration, as well as for the administration in treating drug induced obesity by means of usual processes using auxiliary substances and/or liquid or solid carrier materials.

Hence, in a further aspect the invention also pertains to a pharmaceutical composition containing at least one selective CB₁ antagonistic compound as an active component for the treatment and/or prophylaxis of CB₁ receptor related diseases in juvenile patients and/or for the treatment and/or prophylaxis of drug induced obesity in juvenile as well as adolescent patients, and at least one auxiliary excipient. In such a pharmaceutical composition the selective CB₁ antagonistic compound is preferably present in an amount effectively suited for the treatment and/or prophylaxis of a psychiatric disorder, a gastrointestinal disorder, a cardiovascular disorder, or a combination of said disorders, in a juvenile patient in need of such treating.

In a further embodiment of the invention in the pharmaceutical composition the selective CB₁ antagonistic compound is present in an amount effectively suited for the treatment and/or prophylaxis of drug induced obesity in juvenile as well as adolescent patients in need of such treating.

Finally the invention also includes a method of treatment and/or prophylaxis of CB₁ receptor related diseases in juvenile patients, in particular juvenile obesity, and/or for the treatment and/or prophylaxis of drug induced obesity in juvenile as well as adolescent patients, characterized in that a compound of formula (I) is administered to said patient in need of such treating. The method of treatment and/or prophylaxis according to the invention may be further characterized in that it is a paediatric treating which is directed to psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders and appetite

disorders, neurological disorders such as Parkinson's disease, dementia, distonia, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, ischemia, pain and other CNS-diseases involving cannabinoid neurotransmission, in young patients.

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Preferably, in one embodiment of the invention the method of treatment and/or prophylaxis is directed to the treating of obesity in juvenile patients. In another preferred embodiment of the invention the method of treatment and/or prophylaxis is directed to the treating of drug induced obesity in juvenile or adolescent patients. This drug induced obesity may be in particular caused by drugs like atypical antipsychotics.

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In one embodiment of the invention the method of treatment and/or prophylaxis is directed to the treating of obesity in juvenile patients. Thus, it is advantageous that Cannabinoid antagonists are suitable for the treatment of Childhood Obesity and related Comorbidities as for example Type 2 Diabetes. There is a clear medical need for improved therapy as obesity has become an increasingly important medical problem not only in the adult population but increasingly in children and (young and older) adolescents. In national surveys from the 1960s to the 1990s in the United States, the prevalence of overweight in children grew from 5% to 11% (Sorof and Daniels 2002). In Canada as another example childhood obesity has tripled in the past 20 years (Spurgeon 2002). Obesity in childhood causes a wide range of serious complications, and increases the risk of premature illness and death later in life, raising public-health concerns (Ebbeling, Pawlak et al. 2002). Over the last decades a tremendous increase of cases of type 2 diabetes was observed, especially also in children. This epidemic trend is clearly reflecting the increasing rates of obesity. Type-2-diabetes was in the past considered a disease of adults and older individuals, not a paediatric condition (Arslanian 2002). One of the main risk factor of paediatric type 2 diabetes is obesity.

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Type 2 diabetes in children (as is in adults) is part of the insulin resistance syndrome (Rosenbloom 2002) that includes hypertension, dyslipidemia and other atherosclerosis risk factors, and hyperandrogenism seen as premature adrenarche and polycystic ovary syndrome. Other outcomes related to childhood obesity include left ventricular hypertrophy, nonalcoholic steatohepatitis, obstructive sleep apnea, orthopedic problems, and severe psychosocial problems.

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5 In addition primary hypertension has become increasingly common in children again associated obesity as a major independent risk factor. Obese children are at approximately a 3-fold higher risk for hypertension than non-obese children (Sorof and Daniels 2002). The benefits of weight loss for blood pressure reduction in children have been demonstrated in both observational and interventional studies.

10 Public concerns are rising because of a rapid development of the childhood obesity epidemic in genetically stable populations. Driving factors are assumed to be mainly adverse environmental factors for which straightforward recommendations of life style modifications exists. Obesity and it's related co-morbidities are very serious medical conditions and state of the art measures and treatment of obesity and especially childhood obesity remain largely ineffective at the time being (Ebbeling, Pawlak et al. 2002). The management of type 2 diabetes in is also especially difficult in children and the adolescent age group (Silink 2002). Craving for and over consumption of palatable food is one of the important factors of life-style related obesity in humans and especially also in children and adolescents. Treatment of type 2 diabetes and other co-morbid conditions by the degree of metabolic derangement and symptoms: The only data on the use of oral hypoglycemic agents in children with type 2 diabetes has been with metformin (Rosenbloom 2002).

25 Thus, CB₁ antagonists used according to the present invention offer a unique opportunity for the treatment of obesity by interacting with these "driving forces". They are superior to current medical treatments and especially suited for pediatric treatment because of their outstanding safety profile and/or tolerability. Treatment of obesity especially childhood obesity is besides efficacy dictated by safety.

30 Obesity in childhood is a medical condition that is likely to require long-term management. The safety profile of CB₁ antagonists according to the present invention are suggested to be superior to current standard medications, and these CB₁ antagonists will be especially suited for the treatment and prevention of childhood obesity and related co-morbidities.

35 Literature:

Arslanian, S. (2002). "Type 2 diabetes in children: clinical aspects and risk factors." Horm Res **57 Suppl 1**: 19-28.

40 Ebbeling, C. B., D. B. Pawlak, et al. (2002). "Childhood obesity: public-health crisis, common sense cure." Lancet **360(9331)**: 473-82.

Rosenbloom, A. L. (2002). "Increasing incidence of type 2 diabetes in children and adolescents: treatment considerations." Paediatr Drugs 4(4): 209-21.

5 Silink, M. (2002). "Childhood diabetes: a global perspective." Horm Res 57 Suppl 1: 1-5.

Sorof, J. and S. Daniels (2002). "Obesity hypertension in children: a problem of epidemic proportions." Hypertension 40(4): 441-7.

10 Spurgeon, D. (2002). "Childhood obesity in Canada has tripled in past 20 years." Bmj 324(7351): 1416.

15 In another embodiment of the invention the method of treatment and/or prophylaxis is directed to the treating of drug induced obesity in juvenile or adolescent patients. Drug induced weight gain is also of major concern and subject to high medical need of improved treatments. Again, in this context the
20 CB₁ antagonists according to the present invention are suggested to be superior to current standard medications, and these CB₁ antagonists will be especially suited for the treatment and prevention of drug induced obesity in juvenile as well as in adolescent patients.

25 Regarding drug induced weight gain, it is reported by Zimmermann, U., T. Kraus, et al. (2003, "Epidemiology, implications and mechanisms underlying drug-induced weight gain in psychiatric patients." J Psychiatr Res 37(3): 193-220) that body weight gain frequently occurs during drug treatment of psychiatric disorders and is often accompanied by increased appetite or food craving. While occurrence and time course of this side effect are difficult to predict, it ultimately
30 results in obesity and the morbidity associated therewith in a substantial part of patients, often causing them to discontinue treatment even if it is effective. Weight gain appears to be most prominent in patients treated with some of the second generation antipsychotic drugs and with some mood stabilizers. Marked weight gain also frequently occurs during treatment with most tricyclic
35 antidepressants.

Very large weight gains are associated with drugs like for example the atypical antipsychotics clozapine and olanzapine. Some atypical antipsychotics, however, tend to cause significant weight gain, which may lead to poor compliance and
40 other adverse health effects (Nasrallah, H. (2003). "A review of the effect of atypical antipsychotics on weight." Psychoneuroendocrinology 28 Suppl 1: 83-96.). The mechanisms involved in antipsychotic drug-related weight gain are as

yet uncertain, although serotonergic, histaminic, and adrenergic affinities have been implicated along with other metabolic mechanisms. The atypical antipsychotics vary in their propensity to cause weight change with long-term treatment. Follow-up studies show that the largest weight gains are associated with clozapine and olanzapine, and the smallest with quetiapine and ziprasidone. Risperidone is associated with modest weight changes that are not dose related. Given the equivalent efficacy of atypical antipsychotics, weight-gain profile is a legitimate factor to consider when constructing an algorithm for treatment due to the serious medical consequences of obesity. In this regard co-administration of CB₁ antagonist according to the invention is suggested to work beneficially.

Claims

1. Use of a CB₁ receptor antagonistic compound, prodrugs thereof, tautomers thereof and salts thereof, in the manufacture of medicaments for the treatment and/or prophylaxis of CB₁ receptor related diseases in juvenile patients and/or for the treatment and/or prophylaxis of drug induced obesity in juvenile as well as in adolescent patients:
2. Use of a CB₁ receptor antagonistic compound according to claim 1, wherein the compound is selected from the group of
- 14) Diarylpyrazole selective CB₁ receptor antagonists, preferably the compounds SR-141716A, rimonabant and related compounds, SR-147778, SR-140098 and/or WIN-54461;
 - 15) Aminoalkylindoles selective CB₁ receptor antagonists, preferably the compound lisdopradolone (AM-630);
 - 16) Aryl-aryl substituted benzofuran compounds with selective CB₁ receptor antagonistic activity, preferably the compound LY-320135;
 - 17) Selective CB₁ receptor antagonistic compounds AM251 and/or AM281, and substituted imidazolyl compounds with selective CB₁ receptor antagonistic activity;
 - 18) Azetidine derivatives with selective CB₁ receptor antagonistic activity;
 - 19) The compound CP-55940;
 - 20) Diaryl-pyrazine-amide with selective CB₁ receptor antagonistic activity;
 - 21) The compounds ACPA and ACEA;
 - 22) Pyrazole derivatives with selective CB₁ receptor antagonistic activity;
 - 23) The compounds HU-210 and/or HU-243;
 - 24) The compounds O-585, O-823, O-689, O-1072, and/or O-2093;
 - 25) 3-Alkyl-5,5'-diphenylimidazolidinediones with selective CB₁ receptor antagonistic activity
 - 26) CB₁ antagonistic compounds with selective CB₁ receptor antagonistic activity.
3. Use of a CB₁ receptor antagonistic compound according to claim 1, wherein the use is in the manufacture of a medicament for the treatment and/or prophylaxis of obesity in juvenile patients and/or drug induced obesity in juvenile, as well as adolescent, patients.
4. Use of a CB₁ receptor antagonistic compound according to claim 1, wherein

the use is in the manufacture of a medicament for paediatric treatment and/or prophylaxis pertaining to psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders and appetite disorders, neurological disorders such as dementia, distonia, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, as well as for the paediatric treatment of pain disorders and other CNS-diseases involving cannabinoid neurotransmission, and in the paediatric treatment of gastrointestinal disorders and cardiovascular disorders.

10

5. A pharmaceutical composition containing at least one CB₁ receptor antagonistic compound according to claim 1 or 2 as an active component for the treatment and/or prophylaxis of CB₁ receptor related diseases in juvenile patients and/or for the treatment and/or prophylaxis of drug induced obesity in juvenile as well as adolescent patients, and at least one auxiliary excipient.

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6. A pharmaceutical composition according to claim 5, wherein the at least one CB₁ receptor antagonistic compound is present in an amount effectively suited for the paediatric treatment and/or prophylaxis of a psychiatric disorder, a gastrointestinal disorder, a cardiovascular disorder, or a combination of said disorders, in a juvenile patient in need of such treating.

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7. A pharmaceutical composition according to claim 5, wherein the at least one CB₁ receptor antagonistic compound is present in an amount effectively suited for the treatment and/or prophylaxis of drug induced obesity in juvenile as well as adolescent patients in need of such treating.

25

8. A method of treatment and/or prophylaxis of CB₁ receptor related diseases in juvenile patients (paediatric treating) and/or for the treatment and/or prophylaxis of drug induced obesity in juvenile as well as adolescent patients, characterized in that a CB₁ receptor antagonistic compound according to claim 1 and/or 2 is administered to said patient in need of such treating.

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9. A method of treatment and/or prophylaxis according to claim 8, characterized in that the paediatric treating is directed to psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders and appetite disorders, neurological disorders such as Parkinson's disease, dementia, distonia, Alzheimer's disease, epilepsy, Huntington's disease,

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Tourette's syndrome, ischaemia, pain and other CNS-diseases involving cannabinoid neurotransmission.

5 10. A method of treatment and/or prophylaxis according to claim 8, characterized in that the treating is directed to obesity in juvenile patients.

10 11. A method of treatment and/or prophylaxis according to claim 8, characterized in that the treating is directed to drug induced obesity in juvenile or adolescent patients.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/435 A61K31/4164 A61K31/415 A61K31/4045 A61K31/397 A61K31/352 A61K31/05 A61P3/04 A61P25/18 A61P9/00		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ, MEDLINE, CHEM ABS Data, EMBASE, BIOSIS		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/007887 A (PLUMMER CHRISTOPHER W ;FINKE PAUL E (US); MERCK & CO INC (US); MIL) 30 January 2003 (2003-01-30) cited in the application page 30	1-11
X	US 2001/053788 A1 (TULP MARTINUS T M ET AL) 20 December 2001 (2001-12-20) cited in the application page 2, left-hand column, last paragraph - right-hand column, paragraph 3 claims 1,18-24	1-11
X	WO 03/051851 A (ASTRAZENECA UK LTD ;BERGGREN ANNA INGRID KRISTINA (SE); WILSTERMAN) 26 June 2003 (2003-06-26) cited in the application claims 1,10,13,15	1-11
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<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
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Date of the actual completion of the international search		Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 344 474 B1 (MARUANI JEANNE ET AL) 5 February 2002 (2002-02-05) column 1, line 65 - column 2, line 58	1-3,5,8, 10
X	FR 2 814 678 A (AVENTIS PHARMA SA) 5 April 2002 (2002-04-05) cited in the application abstract claims	1-5,7-11
X	BARTH F: "Cannabinoid receptor agonists and antagonists" EXPERT OPINION ON THERAPEUTIC PATENTS, ASHLEY PUBLICATIONS, GB, vol. 8, no. 3, March 1998 (1998-03), pages 301-313, XP002150850 ISSN: 1354-3776 the whole document	1-3,5-8, 10,11
A	KANYONYO M ET AL: "3-Alkyl-(5,5'-diphenyl)imidazolidinedione s as new cannabinoid receptor ligands" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 9, no. 15, 2 August 1999 (1999-08-02), pages 2233-2236, XP004174166 ISSN: 0960-894X cited in the application the whole document	1-11
A	PERTWEE R G: "Cannabinoid receptor ligands: Clinical and neuropharmacological considerations relevant to future drug discovery and development" EXPERT OPINION ON INVESTIGATIONAL DRUGS 1996 UNITED KINGDOM, vol. 5, no. 10, 1996, pages 1245-1253, XP009026021 ISSN: 1354-3784 table 1	1-11
A	HILLARD CECILIA J ET AL: "Synthesis and characterization of potent and selective agonists of the neuronal cannabinoid receptor (CB1)" JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 289, no. 3, June 1999 (1999-06), pages 1427-1433, XP002270748 ISSN: 0022-3565 the whole document	1-11
	-/-	

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/051976

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>LAN ET AL: "Structure-Activity Relationships of Pyrazole Derivatives as Cannabinoid Receptor Antagonists" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 42, no. 4, 1999, pages 769-776, XP002145465 ISSN: 0022-2623 cited in the application page 769</p>	1-11

INTERNATIONAL SEARCH REPORT

International application No.
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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 8-11
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 8-11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/051976

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03007887 A	30-01-2003	WO 03007887 A2 US 2003114495 A1	30-01-2003 19-06-2003
US 2001053788 A1	20-12-2001	AU 4250101 A BR 0109457 A CA 2401832 A1 CN 1419546 T WO 0170700 A1 EP 1268435 A1 HU 0204519 A2 JP 2004500401 T NO 20024531 A PL 358101 A1 SK 13522002 A3 ZA 200207303 A	03-10-2001 03-06-2003 27-09-2001 21-05-2003 27-09-2001 02-01-2003 28-05-2003 08-01-2004 19-11-2002 09-08-2004 04-03-2003 11-12-2003
WO 03051851 A	26-06-2003	CA 2469786 A1 EP 1458690 A1 WO 03051851 A1	26-06-2003 22-09-2004 26-06-2003
US 6344474 B1	05-02-2002	FR 2758723 A1 AU 6219398 A BR 9806801 A CA 2278661 A1 EE 9900304 A EP 0969835 A1 WO 9832441 A1 HR 980042 A1 ID 22216 A JP 2001501971 T LV 12354 A ,B NO 993634 A SK 99799 A3 TR 9901721 T2 TW 450808 B US 2002128302 A1 ZA 9800691 A	31-07-1998 18-08-1998 16-05-2000 30-07-1998 15-02-2000 12-01-2000 30-07-1998 31-10-1998 16-09-1999 13-02-2001 20-10-1999 27-09-1999 12-06-2000 21-10-1999 21-08-2001 12-09-2002 05-08-1998
FR 2814678 A	05-04-2002	FR 2814678 A1 AT 267595 T AU 9393601 A BG 107739 A BR 0114410 A CA 2424934 A1 CN 1473040 T DE 60103556 D1 DK 1328269 T3 EP 1328269 A2 ES 2217191 T3 WO 0228346 A2 HU 0302044 A2 JP 2004512279 T NO 20031521 A PT 1328269 T SI 1328269 T1 SK 4032003 A3 TR 200401264 T4 US 2002091114 A1	05-04-2002 15-06-2004 15-04-2002 30-01-2004 17-02-2004 11-04-2002 04-02-2004 01-07-2004 20-09-2004 23-07-2003 01-11-2004 11-04-2002 28-11-2003 22-04-2004 24-04-2003 31-08-2004 31-10-2004 11-09-2003 21-07-2004 11-07-2002

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/051976

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 2814678 A		ZA 200303015 A	26-02-2004

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